ABSTRACT

The complexity of glucocorticoid receptor (GR) signaling cannot be measured with direct tissue analysis in living subjects, which has stifled our understanding of GR's role in normal physiology or disease, and the pharmacology of next generation GR modulators. To begin interrogating GR signaling in living subjects, we report herein [18F]-5-(4-fluorobenzyl)-10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinoline ([18F]-YJH08), a radioligand that non-invasively measures GR expression levels in tissues with positron emission tomography (PET). Structurally inspired by a bioactive class of synthetic GR agonists, YJH08 was synthesized in 11 steps to 3% overall yield, and in vitro studies showed it potently binds GR (Kd ~0.4 nM) with ~100-fold selectivity compared to nuclear hormone receptors in the same subfamily. [18F]-YJH08 was prepared via $Cu(OTf)_2(py)_4$-mediated radiofluorination of an arylboronic acid pinacol ester with ~12 % decay corrected radiochemical yield from starting [18F]fluoride ion. Remarkably, [18F]-YJH08 specifically bound GR in virtually all normal mouse tissues, including those for which aberrant GR expression is thought to drive severe diseases (e.g. brain, adipose tissue, kidneys). [18F]-YJH08 also detected GR in a human prostate cancer model, data that suggest the radiotracer could be applied prospectively to find the subset of cancer patients that might benefit from the GR antagonists currently in clinical trials for this malignancy. In summary, [18F]-YJH08 enables a quantitative assessment of GR expression levels in real time among multiple tissues simultaneously, and this technology is a first step toward unraveling the daunting complexity of GR signaling in vivo.